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Detection of Early Ethambutol Ocular Toxicity: Ishihara Pseudoisochromatic Plates versus the Farnsworth D-15 Hue Test

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Abstract

Purpose: The aim of this study was to compare the efficacy of the Farnsworth D-15 hue test in detecting early ethambutol toxicity compared to the Ishihara pseudoisochromatic plates.

Methods: This retrospective study was conducted at the Department of Ophthalmology, Caritas Medical Centre in Hong Kong from January 2012 to April 2013. Medical records for consecutive patients with tuberculosis referred for suspected ethambutol-induced toxic optic neuropathy were reviewed. All consenting subjects underwent both the Ishihara pseudoisochromatic plates and the Farnsworth D-15 hue test. Those with pre-existing optic neuropathies, poor visual acuity, significant cataract, known congenital colour vision defects, retinopathies, and those on other systemic medications with potential ocular toxicity side effects were excluded. The qualitative results for the 2 screenings tests were compared.

Results: During the study period, 65 eligible subjects, with tuberculosis, prescribed with ethambutol, were recruited. On Ishihara pseudoisochromatic plates testing, all (100%) of the subjects had normal results. On Farnsworth D-15 hue testing, 23.1% (15/65) had abnormal results: 12.3% (8/65) had a tritan (blue-yellow) defect and 10.8% (7/65) had non-specific colour defects not conferring to a single colour deficiency.

Conclusion: The Farnsworth D-15 hue test appears to be more sensitive than the Ishihara pseudoisochromatic plates in detecting colour defects as an initial subjective screening tool for suspected ethambutol-related optic neuropathy.

Keywords: Ethambutol; Farnsworth D-15 hue test; Ishihara pseudoisochromatic plates; Tuberculosis

Introduction

Tuberculosis remains an important infectious disease in Hong Kong Special Administrative Region, China. Although the incidence is on a decreasing trend, from 97.9 cases per 100000 people in 2002 to 69.6 in 2012,[1] the incidence is still higher than in Europe and America, where the incidence was 42 and 28 cases per 100,000 people respectively[2].

Ethambutol is one of the most commonly prescribed anti-tuberculosis medications in Hong Kong. The drug has been well associated with ocular toxicity manifesting as optic neuropathy since its first use in the 1960's[3,4]. Ethambutol-induced optic neuropathy is duration and dose dependent, although rare cases of idiosyncratic reaction presenting days after the commencement of a standard dose have been reported[5,6]. Symptoms of toxicity does not usually occur until 1.5 months after the initiation of therapy[7]. The reported incidence of toxicity is 18% in those with a daily dose > 35 mg/kg, 5-6% in those with 25 mg/kg, and approximately 1% with a daily dose of 15 mg/kg for 2 months or more[4,8,9]. In Hong Kong, the standard daily dose is15 mg/kg for the treatment of pulmonary tuberculosis. At this dosage, toxic optic neuropathy is uncommon.

Signs and symptoms of ethambutol-induced optic neuropathy can be subtle or even subclinical in the early stage. Colour vision abnormality (dyschromatopisa) is one of the first detectable signs. Blue-yellow (tritan) defects occur earlier on whilst red-green (protan) defects develop later on in the course of the toxicity[10,11,12]. As the visual impairment caused by ethambutol toxicity may not be completely reversible,[13,14,15] early detection and prompt cessation of the drug is essential to avoid significant permanent visual impairment.

Figure 1.1: Farnsworth D-15 hue test set with 15 coloured caps with a natural hue progression

Figure 1.2: Patients are asked to select a coloured cap that most closely resembled the hue of the reference cap.

Figure 1.3: All 15 caps are arranged in sequence based on the patient's perception of colour.

Figure 1.4: After completing the task, the wooden box is flipped over and the corresponding numbers are shown.

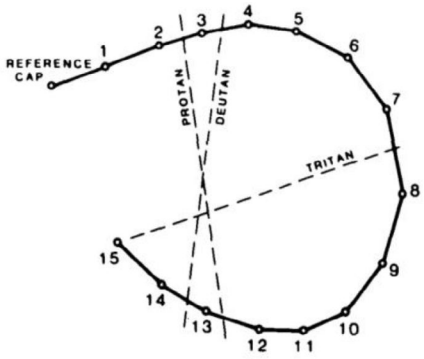

Figure 2.1: Normal result – no cross-lines

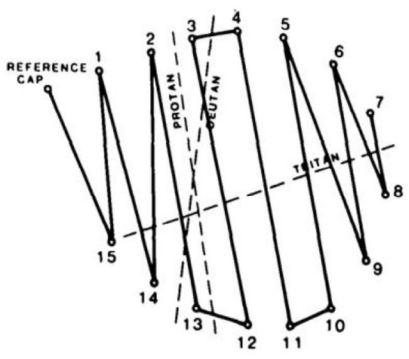

Figure 2.2: Protanope – cross-lines parallel to protan axis

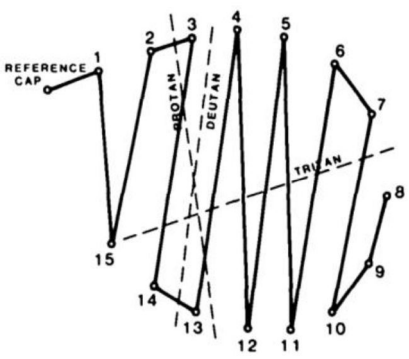

Figure 2.3: Deutanope – cross-lines parallel to duetan axis

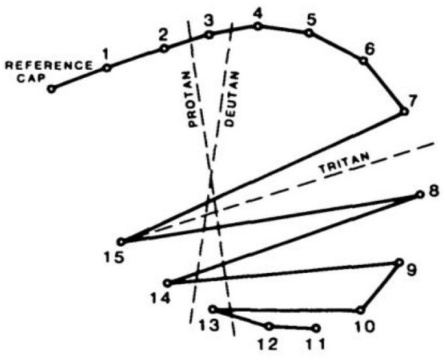

Figure 2.4: Tritanope – cross-lines parallel to tritan axis

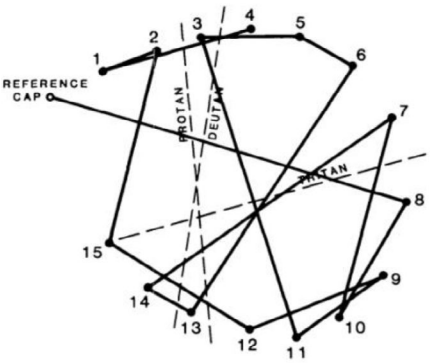

Figure 2.5: Non-specific color vision defect – cross-lines do not obey any axis

Ishihara pseudoisochromatic plates are commonly used for the screening of colour vision defects in patients with suspected ethambutol toxicity due to the wide availability, ease of use of the plates and the traditional belief that acquired optic neuropathies generally cause protan defects. As Ishihara pseudoisochromatic plates are mainly designed to detect protan colour defects, it may not be the most ideal assessment tool for ethambutol toxicity that manifest with a tritan colour defect.
The Farnsworth D-15 hue test is a simplification of the Farnsworth-Munsell 100 hue test with fewer coloured caps to rearrange and hence requires less testing time. The Farnsworth D-15 hue test is conducted under natural day light and subjects are asked arrange a series of coloured caps based on the ability to appreciate similarities in colour shades (Fig 1.1-1.4). The results are compared to the reference sequence in order to categorize the different types of colour defects into protan, deutran, or tritan16 (Fig. 2.1-2.5).

The aim of this study was to compare the efficacy of the Farnsworth D-15 hue test in detecting early ethambutol toxicity compared to the Ishihara pseudoisochromatic plates.

Methods

This retrospective study was conducted at the Department of Ophthalmology, Caritas Medical Centre in Hong Kong Special Administrative Region, China from January 2012 to April 2013. Medical records of consecutive patients with tuberculosis who were referred to our unit for suspected ethambutol toxicity (usually presenting with visual blurring) were reviewed. All consenting subjects underwent both the Ishihara pseudoisochromatic plates and the Farnsworth D-15 hue test. The exclusion criteria included: subjects with pre-existing optic neuropathies (glaucoma, optic nerve compression, ischemic optic neuropathy, or optic neuritis); poor visual acuity inhibiting the appreciation of the first Ishihara test page; significant cataract (especially the nuclear sclerosis type that could affect color vision); known congenital colour vision defects; retinopathies; and those who were on other systemic medications with the potential for optic neuropathy toxicities including digitalis and amiodarone.

The Ishihara pseudoisochromatic plates test was performed as follows: the first 17 plates were presented to the patient at a distance of 75cm; subjects that were unable to read at least 9 of the 17 plates in either eye were labeled as "optic neuropathy suspects".

The Farnsworth D-15 hue test was done by a single orthoptist. All 15 colored caps were randomly set on a table. Subjects were asked to select a colored cap that most closely resembled the shade of the reference cap. Subjects then continued to arrange the rest of the colored caps in sequence of resembling shades. The investigator scored the test by referencing the sequence of numbers on the back of each cap and plotted the sequence onto a score sheet. If the sequence was correct from 1 through 15, a circle was formed on the score sheet. If the sequence deviated from the reference, cross-lines were formed suggesting either a protan, deutran, or tritan defect (Figures 2.1 to 2.5). The test was completed within a time frame of 2 minutes. Test results were interpreted by 2 investigators in addition to the testing orthoptist. Those who had cross-lines on the score sheet were also labeled as "optic neuropathy suspects".

All optic neuropathy suspects were arranged with additional tests including Humphrey Visual Field and Optical Coherence Tomograph (OCT) for the retinal nerve fibre layer thickness for definitive confirmation of toxic optic neuropathies. Whilst waiting for these investigations, physicians were also informed of the possibility of ethambutol toxicity and where appropriate, ethambutol was stopped after consideration of the risks and benefits.

Results

During the study period, 71 subjects, all with tuberculosis infection prescribed with ethambutol, were referred to our unit for suspected ethambutol toxicity. Six were excluded from this study (2 had glaucoma, 2 had poor vision from cataract, 1 had epiretinal membranes over both maculas, and 1 had congenital colour vision deficiency).

Sixty-five subjects were eligible for the study. On Ishihara pseudoisochromatic plates testing, all (100%) of the subjects had normal results. On Farnsworth D-15 hue testing, 23.1% (15/65) were labeled as optic neuropathy suspects; of which, 12.3% (8/65) had a tritan defects whilst 10.8% (7/65) had non-specific colour defects not conferring to a single colour defect. The physicians were notified of the abnormal Farnsworth D-15 hue test results whilst the subjected waited for objective assessments.

Discussion

Tuberculosis is a relevant infectious disease in our locality and suspected toxicities with ethambutol is not uncommonly encountered. Currently, patients with suspected ethambutol toxicity are referred to ophthalmology units for screening. Prior to the arrangement of more definitive objective assessments for toxic optic neuropathy like visual field or OCT, subjective tests are use to test for dyschromatopsia since tritan defects are one of the first signs of acquired toxic optic neuropathy[10,11,12]. The Ishihara pseudoisochromatic plates are one of the most commonly used screening tools but as we have demonstrated, the detection rate of dyschromatopisa in 65 with suspected ethambutol toxicity was zero. However, on the same population, the Farnsworth D-15 hue test detected dyschromatopisa in 23.1% of subjects, of which 12.3% were confirmed to have tritan defects compatible with toxic optic neuropathy. We postulate that the suboptimal detection rate in the Ishihara pseudoisochromatic plates is primarily due to the fact that the plates are designed to detect for protan anomalies that usually manifest in more advanced toxic optic neuropathy[10,11,12]. It is important however, to note that the decision to stop ethambutol should not solely rely on the results of a single subjective, but rather a mutli-disciplinary consideration of symptoms, subjective and objective tests, and liaison with physicians on the risks and benefits of stopping treatment. However, it is imperative to keep in mind that detection from objective investigations like visual field or OCT may be limited in the early stages of toxicity,[18] thus, in real clinical practice, clinicians are often faced with the clinical decision to determine the likelihood of toxicity based on subjective colour vision testing and in such cases, Farnsworth D-15 hue test

seems superior to the Ishihara pseudoisochromatic plates.

Our study had its limitations. Firstly, all subjects presented to our unit for the first time for the screening of ethambutol ocular toxicity and no baseline colour vision tests were available. Secondly, all patients were also concomitantly on isoniazid as combination therapy for tuberculosis which can also potentially cause optic neuropathy although reports on the frequency of isoniazid toxicity are lacking in the literature and likely to be less frequent than ethambutol[17]. Thirdly, both tests were highly subjective, based on the intelligence and comprehensibility of subjects but as the aim of this study was to compare between these 2 subjective assessments, both tests were subjected to the same confounding factor. Fourthly, it is our understanding than many of the 15 subjects with abnormal Farnsworth D-15 hue test results had their ethambutol immediately stopped by the physicians in order to minimize the risk of toxicity hence many of them did not have their objective tests completed. Lastly, we only included subjects with suspected ethambutol toxicity, future studies including normal subjects as controls would help to eliminate all bias.

Conclusion

The Farnsworth D-15 hue test appears to be more sensitive than the Ishihara pseudoisochromatic plates in detecting colour defects as an initial assessment for ethambutol-related optic neuropathy.

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